# Clinical and histopathologic features of colorectal adenocarcinoma in crohn's disease

Galata, Christian ; Hirsch, Daniela ; Reindl, Wolfgang ; Post, Stefan ; Kienle, Peter ; Boutros, Michael ; Gaiser, Timo ; Horisberger, Karoline

Abstract: GOALS: The aim of this study was to assess the histopathologic characteristics of colorectal carcinomas (CRC) in patients with Crohn's disease (CD). BACKGROUND: A higher frequency of microsatellite instability (MSI) is seen in mucinous compared with nonmucinous CRC which suggests that its pathogenesis involves distinct molecular pathways. Several publications reported a higher percentage of mucinous adenocarcinoma in CD patients with CRC. So far, there has been no investigation of MSI in CD patients with mucinous CRC. STUDY: The medical records of patients who underwent surgery for CRC were reviewed and those with a history of CD identified. The data of histologic classification and MSI status of the tumor were investigated. RESULTS: Fourteen patients with CD-associated CRC were identified (5 female, 9 male) resulting in 20 CRC in total. Histologic investigation revealed 7 adenocarcinomas without a mucinous or signet ring cell component. All other CRCs harbored a mucinous (n=11) and/or signet ring cell (n=6) component. All tumors assessed for MSI were found to be microsatellite stable. CONCLUSIONS: Our data indicate that CRCs with signet ring cell and mucinous components were much more common in patients with CD than in patients with sporadic CRC. This observation suggests that CRC in CD represent an own entity with distinct histopathologic and molecular features. This may implicate potential consequences for diagnosis and therapy of CRC in CD in the future as well as new factors to identify patients with an increased risk for developing CRC in CD.

DOI: https://doi.org/10.1097/MCG.0000000000000817

# Clinical and Histopathologic Features of Colorectal Adenocarcinoma in Crohn's Disease

*Christian Galata, MD,* Daniela Hirsch, MD,† Wolfgang Reindl, MD,‡ Stefan Post, MD,* Peter Kienle, MD,* Michael Boutros, PhD,§‖ Timo Gaiser, MD,† and Karoline Horisberger, MD*¶*

**Goals:** The aim of this study was to assess the histopathologic characteristics of colorectal carcinomas (CRC) in patients with Crohn's disease (CD).

**Background:** A higher frequency of microsatellite instability (MSI) is seen in mucinous compared with nonmucinous CRC which suggests that its pathogenesis involves distinct molecular pathways. Several publications reported a higher percentage of mucinous adenocarcinoma in CD patients with CRC. So far, there has been no investigation of MSI in CD patients with mucinous CRC.

**Study:** The medical records of patients who underwent surgery for CRC were reviewed and those with a history of CD identified. The data of histologic classification and MSI status of the tumor were investigated.

**Results:** Fourteen patients with CD-associated CRC were identified (5 female, 9 male) resulting in 20 CRC in total. Histologic investigation revealed 7 adenocarcinomas without a mucinous or signet ring cell component. All other CRCs harbored a mucinous (n = 11) and/or signet ring cell (n = 6) component. All tumors assessed for MSI were found to be microsatellite stable.

**Conclusions:** Our data indicate that CRCs with signet ring cell and mucinous components were much more common in patients with CD than in patients with sporadic CRC. This observation suggests that CRC in CD represent an own entity with distinct histopathologic and molecular features. This may implicate potential consequences for diagnosis and therapy of CRC in CD in the future as well as new factors to identify patients with an increased risk for developing CRC in CD.

**Key Words:** Crohn's disease, mucinous adenocarcinoma, microsatellite instability

(*J Clin Gastroenterol* 2017;00:000–000)

The association of colorectal carcinomas (CRC) with inflammatory bowel disease is well established for ulcerative colitis (UC),[1] though recent data suggest that it might have been overestimated in the past or it might be decreasing.[2] The carcinogenic risk for Crohn's disease (CD) is less investigated and thus, its magnitude remains controversial. The descriptions range from no increased CRC compared with the normal population risk up to being comparable with the CRC risk in UC.[1,3–6] In terms of prognosis a recent meta-analysis showed a trend toward an adverse prognosis in patients with CRC and CD compared with sporadic CRC patients.[7] The last ECCO workshop of the European Crohn's and Colitis Organization on CRC in inflammatory bowel disease confirmed a worse outcome in this population.[2]

## HISTOLOGIC SUBTYPES OF COLORECTAL ADENOCARCINOMA

Mucinous adenocarcinoma (MAC) is a histologic subtype of CRC where secreting acini produce large pools of extracellular mucus as the predominant component of the carcinoma. Mucinous accounts for 5% to 15% of all CRC, while some authors describe in smaller series even lower and higher rates.[8–10] The World Health Organization (WHO) defines adenocarcinoma as mucinous when >50% of the lesion is extracellular mucus. If <50% but >10% of the lesion is composed of mucus it is designated as adenocarcinoma with mucinous component. Several publications have reported a higher percentage of MAC in CD patients with CRC; however, the magnitude of this varies considerably.[11–13]

Signet ring cell carcinoma (SRCC) is a less frequent entity. The WHO describes SRCC as a carcinoma composed of >50% signet ring cells, which are defined by an accumulation of intracellular mucin. A CRC where <50% but >10% of the lesion is composed of signet ring cells is defined as CRC with signet ring component. In the National Cancer Data Base (NCDB) of the American College of Surgeons and the American Cancer Society, 1% of the patients with sporadic CRC show a SRCC.[10] Although older data indicate a much higher proportion of SRCC in CD,[12] a more recent study failed to confirm these results.[11]

Both forms (MAC and SRCC) have been reported to involve poorer prognosis to a different extent. Although MAC of the colon did not show any different prognosis to non-MACs in the NCDB analysis, MACs of the rectum showed a significantly worse prognosis compared with nonmucinous rectal cancer.[10] This may be related to the fact that MACs showed a poorer response to neoadjuvant chemoradiation than nonmucinous CRC, a treatment regularly applied in rectal cancer.[14,15] In a meta-analysis, a mucinous component in adenocarcinoma was also negatively correlated with survival.[16] SRCCs are associated with a higher risk of death compared with nonmucinous,

Received for publication June 26, 2016; accepted December 30, 2016.
From the *Department of Surgery; †Institute of Pathology; ‡Department of Internal Medicine III, Medical Faculty Mannheim, Heidelberg University, Germany; §Division Signaling and Functional Genomics, German Cancer Research Center (DKFZ); ‖Department of Cell and Molecular Biology, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany; and ¶Department of Visceral and Transplant Surgery, University Hospital Zurich, Zurich, Switzerland.
C.G. and D.H. contributed equally.
The authors declare that they have nothing to disclose.
Address correspondence to: Karoline Horisberger, MD, Department of Surgery, University Hospital Mannheim, Faculty of the University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany (e-mail: karoline.horisberger@gmx.de).

DOI: 10.1097/MCG.0000000000000817

non–signet ring cell adenocarcinomas in both colon and rectum.[10]

In this study, we present the clinical and histopathologic data of CRC patients with CD in a single-center database.

## METHODS

The study protocol was reviewed and approved by the local institutional ethics committee (2013-570N-MA, 2013-821R-MA). The study was performed according to the Declaration of Helsinki.

### Patients

A retrospective analysis of the surgical database for CRC at our institution was performed. The medical records of 2067 patients who underwent surgery for CRC between 01/1999 and 12/2015 were reviewed and those with a history of CD were identified. The data were evaluated with regard to characteristics of CD as well as CRC.

### Pathology Investigation

Two pathologists (T.G., D.H.) examined hematoxylin and eosin-stained sections of each case. Histologic grading according to WHO classification for CRC (not otherwise specified) was performed.[17]

### Microsatellite Instability (MSI)

MSI phenotype was detected indirectly by loss of DNA mismatch repair protein expression (immunohistochemistry) and directly by microsatellite analysis [pathological complete remission (PCR)].

### MSI Detection (Immunohistochemistry)

Tissue sections of 2 to 3 μm were mounted on self-coated slides followed by the semiautomatic process of deparaffinization and epitope retrieval as published previously.[18] Primary antibodies were then applied targeting the epitopes MSH2, MSH6, MLH1, and PMS2 (all DAKO, MLH1: 1:50; MSH2: 1:100; MSH6: 1:10; PMS2: 1:100). Antibody binding was visualized using the Envision System as described by the manufacturer (DakoCytomation, Glostrup, Denmark). Only slides with distinct positive nuclear staining in the basal crypt cells of normal mucosa and stromal and inflammatory cells were evaluated. Tumor samples lacking nuclear staining MSH2, MSH6, MLH1, and/or PMS2 were considered MSI.

### MSI Detection (PCR)

Histology-based macrodissected tumor areas and normal tissue were selected and digested using proteinase K. DNA was extracted according to conventional protocols.[19] For microsatellite analyses, we used a panel of 8 well-established pairs of microsatellite primers that consisted of 5 mononucleotid (BAT26, BAT25, NR21, NR24, MONO27) and 3 dinucleotid (D2S123, D5S346, D17S250) repeat markers. The primer sequences for the amplification of microsatellite repeats were retrieved from the Genome Data Base. MSI was detected as the appearance of PCR bands of different lengths in tumor tissue not seen in the genomic DNA from normal tissue. Tumor was considered microsatellite stable (MSS) if none of the 8 PCRs showed band shift. MSI-low was defined as instability in only 1 marker; high MSI (MSI-H) as instability in >1 marker and if no marker showed instability the tumor was considered MSS.

## RESULTS

### Patients

Fourteen patients with CD undergoing surgery for CRC were identified. The patients' characteristics are displayed in Table 1. One patient had concomitant primary sclerosing cholangitis. None of the patients had a family history suspicious to hereditary colorectal cancer. The use of Crohn's medication was difficult to trace completely in the retrospective data collection. Most of the patients had a treatment with 5-aminosalicylic acid, medication with other drugs cannot be reported conclusive. At the time of diagnosis, the patients in median had a 26-year history of CD. One patient with simultaneous diagnosis of CD and CRC showed symptoms for >10 years, during which time he was treated for irritable bowel syndrome. Diagnosis was delayed because the patient never agreed to a colonoscopy until symptoms were beyond all bearing. Because of the discrepancy between symptoms and diagnosis, this patient was excluded from the calculation of median duration of CD before diagnosis of CRC. Twelve patients underwent tumor resection according to oncologic principles and all but 1 tumor were resected in sano (R0). Two patients underwent only exploration and adhesiolysis when peritoneal carcinomatosis became evident.

From a total of 20 CRCs in 14 patients, histologic grading could be undertaken in 16. In 4 CRC, grading could not be estimated: 2 of these patients had undergone neoadjuvant treatment; tumor regression grade was 3 according to the Dworak classification system in both cases. The 2 other patients showed peritoneal carcinomatosis and only biopsies were taken (one of them also had preoperative chemoradiation); no T stage and no N stage could be defined in these 2 patients, too. In 1 patient, no lymph nodes could be retrieved; this patient previously underwent sphincter-preserving proctocolectomy due to Crohn's colitis; 18 years later, the subsequent rectal cancer in the rectal stump was diagnosed.

Three patients had synchronous CRC. One patient had 4 carcinomas in 3 localizations, 1 patient 3 synchronous carcinomas in 2 different colon segments, 1 patient 2 carcinomas in different localizations.

One tumor (6.25%) showed good differentiation (G1), 6 (37.5%) were moderately differentiated (G2), and 9 (56.25%) were poorly differentiated (G3).

Localization of CRC can be seen in Table 2. Three patients had synchronous CRCs in different localizations. In 1 patient, concomitant adenocarcinomas of the ascending colon and hepatic flexure were present. In another

**TABLE 1.** Patients' Characteristics

| Characteristics | n = 14 |
|---|---|
| Age (y) (median; range) | 50.5 (28-76) |
| Sex (male/female) | 9/5 |
| Age at diagnosis of Crohn's disease (y) (median; range) | 22.5 (12-58) |
| Duration of Crohn's disease (y) (median; range) | 26 (4-41) |
| Crohn's colitis [n (%)] | 8 (57.1) |
| Patients with synchronous colorectal carcinomas at different localizations [n (%)] | 3 (21.4) |
| Patients with history of colorectal cancer (Metachronous colorectal cancer) [n (%)] | 1 (7.1) |
| History of ileocecal resection [n (%)] | 4 (28.6) |

**TABLE 2.** Distribution of Tumor Localizations and Histopathologic Stages

| Distribution of Tumor Localizations (n = 20) | n (%) |
|---|---|
| Right hemicolon | 6 (30) |
| Transverse colon | 2 (10) |
| Left hemicolon | 0 (0) |
| Sigmoid | 3 (15) |
| Rectum | 6 (30) |
| Fistula-in-ano cancer | 3 (15) |
| Histopathologic tumor stage | |
| T1 | 1 (5) |
| T2 | 6 (30) |
| T3 | 5 (25) |
| T4 | 6 (30) |
| Tx | 2 (10) |
| Histopathologic lymph node stage | |
| N0 | 14 (70) |
| N1 | 1 (5) |
| N2 | 2 (10) |
| Nx | 3 (15) |

patient, 4 different carcinomas were found in 3 localizations: 1 in the ascending colon, 2 in the transverse colon, and 1 in the rectum. At least, 1 patient simultaneously had 3 carcinomas: 1 in the ascending colon and 2 in the sigmoid colon. In addition, this patient had diagnosis of CD and CRC at the same time. Before surgery, preoperative diagnosis of a high-grade intraepithelial neoplasia in a stenosis of the sigmoid colon was established and suspicion of CD arose from an additional detectable conglomerate tumor between sigmoid colon and terminal ileum. Radical resection was performed for the sigmoid colon and due to the conglomerate tumor an ileocecal resection was performed, too. However, the latter resection was not performed according to oncologic standards. On subsequently histologic work-up, all of the carcinomas were resected in sano (R0). The patient subsequently received an oncological salvage resection of the right hemicolon without any further signs of a tumor or infiltrated lymph nodes. Histopathologic stages of all patients can be seen in Tables 2 and 3.

Ongoing active inflammation was seen in 8 patients; in another 3 patients only moderate or discontinuous inflammation was diagnosed. In 2 cases, information on inflammatory activity was not retrievable from the pathology or colonoscopy reports. The absence of any signs of ongoing inflammation was reported in 1 patient.

Neoadjuvant chemoradiation was applied in 3 patients; 1 of them was subsequently diagnosed with peritoneal carcinomatosis during surgery; no resection was performed. Radical resection could be performed in the other 2 patients.

Indication for adjuvant chemotherapy was confirmed in 7 cases; however, only 4 patients received postoperative chemotherapy due to anastomotic leakage in 1 case and wound breakdown in the other 2.

Palliative chemotherapy was planned in 2 cases with peritoneal carcinomatosis; one of the patients deceased before treatment initiation.

Four patients deceased during follow-up due to progress of the malignant disease (Table 4).

**TABLE 3.** Systemic Tumor Burden of the Patients (n = 14)

| Distant Metastasis at Primary Surgery With Regard to Patients (n = 14) | n (%) |
|---|---|
| M0 | 10 (71.4) |
| M1 | 4 (28.6) |
| Mx | 0 |
| UICC classification (n = 14) | |
| UICC I | 2 (14.3) |
| UICC II | 5 (35.7) |
| UICC III | 3 (21.4) |
| UICC IV | 4 (28.6) |

UICC indicates Union internationale contre le cancer.

**TABLE 4.** Follow-up Results

| Follow-up Results (n = 14) | Median (Range) Mean (STD) |
|---|---|
| Follow-up (mo) | 14.5 (1-60) |
| | 24.8 (± 22) |
| Progression-free survival (mo) | 14.5 (0-60) |
| | 22.4 (± 22.5) |
| Overall survival (mo) | 14.5 (1-60) |
| | 24.8 (± 22) |
| | n (%) |
| Local recurrence | 0 |
| Distant metastasis | 4 (28.6) |
| Cancer-related death | 4 (28.6) |

## Histopathologic Evaluation and MSI Status

Histologic investigation confirmed 7 of 18 cases (38.9%) as an adenocarcinoma without mucinous or signet ring cell component (Table 5). The paraffin blocks of 2 tumors were not available for investigation.

All other tumors were classified as CRCs with mucinous and/or signet ring cell component. We refrained from using the terms "mucinous adenocarcinoma" and "signet ring cell carcinoma" in the histologic classification of the CD-associated CRCs because for 2 patients only biopsy material was available, which did not allow an accurate quantification (>/< 50%) of the extracellular mucin pools as is required by the WHO classification. In the analysis of MSI status, no tumor showed MSI.

## DISCUSSION

We present a single-center study of a tertiary referral center on clinical and histopathologic characteristics of CRC in CD. The risk for development of CRC in CD is still controversial and there is no scientific evidence to define surveillance intervals in CD. Current treatment guidelines in Germany recommend regular surveillance colonoscopies at least every 2 years beginning from the eighth year of CD—but solely for patients with extensive Crohn's colitis.[20] The definition of extensive colitis is according to the Montreal classification for UC what means that the

**TABLE 5.** Histopathologic Characteristics

| Tumor Characteristics | n (%) |
|---|---|
| CRC with mucinous component | 11 (61.1) |
| CRC with signet ring cell component | 6 (33.3)* |
| CRC without mucinous or signet ring cell component | 7 (38.9)* |

*Combination of mucinous and signet ring cell components in 6 patients.

CRC indicates colorectal carcinomas.

involvement of the colitis extends proximal to the splenic flexure.[21] For CD patients without colitis, surveillance recommendations are not given. Five of the patients in our cohort had the screening colonoscopies as for the normal population at the age over 50.

The frequency of CRCs decreases in patients without reference to CD from the rectum to proximal localizations. In CD patients, a specific anatomic distribution of CRC has not yet been described. Some authors describe a predominance of rectal cancer[22]; others have reported a 2-peak distribution in the right hemicolon as well as in the rectum, but much less in the left hemicolon.[11] This distribution was also seen in our cohort. However, it was not possible to establish a correlation between the localization of the carcinoma and disease-free survival as some of the patients had synchronous carcinomas in different segments and furthermore the numbers are too low to allow any meaningful conclusions.

We found interesting histopathologic and molecular features that set CRC in CD apart from sporadic CRC.

First, adenocarcinomas with a mucinous component are overrepresented in our cohort of colorectal cancers. In nonselected CRC collectives the frequency of CRCs with mucinous phenotype varies between 5% and 15%[10]; in our series we found 61% MACs.

In 2007 Svrcek et al[11] reported one of the rare studies on the incidence of MAC in CD patients. Their findings concerning patient's age, duration of CD as well as distribution of the carcinoma in the colorectum were quite similar to our results. Earlier studies reporting CRC in CD patients also displayed a higher proportion of MAC.[12,23] In 2010, Ouaïssi et al[24] reported 14 cases of colorectal adenocarcinoma in CD patients; 35% of them showed mucinous differentiation. In a recently published study of 5 colorectal adenocarcinomas in CD patients all showed mucinous histopathology.[13] However, in this study all patients had in the past already undergone total colectomy and then had a fistula-in-ano cancer. The significantly higher number of MAC on the basis of chronic perianal fistula is known.[22,25,26] In our cohort, 2 of the 3 patients with fistula-in-ano cancer showed a mucinous differentiation.

The higher incidence of MAC in CD patients could be correlated to the higher incidence of right-sided colon cancer. In a meta-analysis including 20 studies MAC in general is more often localized proximal to the splenic flexure and less common in male patients.[16] A recently published large single-center study confirmed the findings of more right-sided colon cancer with mucinous histopathology.[27] We evaluated 11 adenocarcinomas with a mucinous component in our cohort. Only 2 were situated proximal to the splenic flexure.

Second and most striking is the negative correlation of MAC and MSI in CD patients.

MSI, which is found in 15% to 20% of sporadic CRC, reflects the inactivation of DNA mismatch repair.[28,29] In nonpreselected CRC series, MAC include between 30% and 60% MSI cases[30–32]; in the few existing studies, SRCC shows MSI rates of 31% to 38%.[32,33] In general, distinctive features including a better prognosis have been demonstrated for CRC when MSI is present.[34] However, this contrasts with the more advanced status of MAC at diagnosis and the worse survival of patients with mucinous rectal cancer and signet ring cancer in both colon and rectum in large studies.[10,32] In view of the heterogenous data in the literature, a definite conclusion concerning the clinical influence of MSI in MAC cannot be drawn.[16,35] A recently published study failed to show that MSI status is relevant for prognosis in colorectal SRCC—probably due to limited statistical power.[35]

Generally, a higher frequency of MSI has been reported for mucinous (27% to 36%) compared with non-MAC of the colorectum (about 15%).[31,32,34,36,37] This correlation of MAC and MSI is already established in such a way that analysis of MSI status has been integrated in guidelines.[38]

In non-MAC, MSI-H is linked to a better prognosis than microsatellite stability.[34] The association of MSI-H with less aggressive tumor growth, lower tumor stage, and better outcome is also assumed for MAC.[30,35,37,39] However, the heterogenous data prevent conclusive statements. Four publications could be retrieved for a meta-analysis containing data on survival in MAC, stratified by MSI Status.[16,30,31,39,40] Three of them could show a better survival for MSI high in MAC compared with MSS-MAC.[16,30,31,40] However, 1 study showed a worse survival in MSI-MAC.[39]

Against this background, it is of particular interest that none of the MACs identified in CD in the presented study displayed MSI. The study by Malvi et al[13] on 5 fistula-in-ano cancers had the same findings. However, the description of a clearly increased rate of MAC and SRCC in CD patients with colon or rectal cancer and the correlation to a so far not explainable high rate of MSS in both colon and rectal cancer has not been made yet.

Although the higher percentage of MSI-H in MAC independent from CD suggests that its pathogenesis might involve distinct molecular pathways,[34] the finding in CD patients raises the question of another specific pathogenesis. The higher percentage of MSS status in MAC of CD patients has not yet been investigated. Svrcek et al[11] described a higher frequency of MAC in colorectal cancer of CD patients but completely missed to investigate the MSI status.

The third issue concerns the high percentage of carcinomas with a signet ring cell component in our cohort. SRCC was first described by Parham[41] in 1923 as a subtype of CRC that accounts for only 1% of CRC. SRCC is associated with an advanced tumor stage at diagnosis and a lower survival rate compared with mucinous and non-mucinous CRC in both colon and rectum.[9,10] On an average, patients with signet ring cell adenocarcinoma of the colorectum are younger than other CRC patients.[10] As in mucinous adenocacinoma, SRCC tend to be in the right hemicolon more often.[10] Our cohort included 6 patients with CRC with a signet ring cell component. One of them was in the cecum, the others were located in the sigmoid (n = 1) or in the rectum (n = 4).

An interesting publication by Börger et al[42] showed that signet ring cells within mucinous carcinomas correlate with increased T stage and poorer prognosis. A just recently published study showed that even a minor signet ring cell component is correlated to higher mortality in colon adenocarcinoma but not in rectal cancer.[35] MSI-H rates are described to be higher in SRCC of the colorectum.[32]

A comparison with former results of SRCC in CD is not possible as this is, to the best of our knowledge, the first such report. According to this, no comparison with MSI rates in CD patients with SRCCs of the colorectum can be drawn but it brings again to mind that pathogenesis of CRC in CD patients might be dissimilar from other sporadic CRC.

In a meta-analysis mucinous colorectal adenocarcinoma showed a slightly worse survival rate than non-MAC with a hazard ratio of 1.06[16]

In fact, mucinous CRCs are often diagnosed at a more advanced stage and most of the earlier studies suggesting an adverse prognosis for MAC did not analyze stage-by-stage.[10] A large study of the NCDB including 250,000 patients indicated that MACs have a worse prognosis in the rectum but not in the colon.[10] This could reflect its poorer response to neoadjuvant treatment, which is applied in the rectum but not in the colon.[14]

Comparison in non–CD-related sporadic MACs and SRCCs show that MACs are less responsive to chemotherapy[43,44] as well as to chemoradiation than non-mucinous non–signet ring cell CRC.[15] As far as we know SRCC seems to have a comparable benefit from chemotherapy as common colorectal adenocarcinomas.[45] We cannot comment on response to neoadjuvant or adjuvant treatment from our data as only 3 patients underwent neoadjuvant chemoradiation. One of them showed devastating progress under treatment.

The course of CRC patients with CD seems to be significantly worse than that of other CRC sporadic patients.

In our cohort, median age was 50.5 years at the time of CRC diagnosis; compared with epidemiologic data for Germany, this is >20 years below the average age of all patients diagnosed with sporadic CRC.[46] Moreover, after a follow-up of 18 months more than one quarter of the patients (n = 4; 28.6%) had distant metastasis and died from cancer.

A publication by Ekbom et al[47] from 1990 including 12 cases of CRC in CD showed a higher risk for developing CRC in patients with an early onset of CD. However, a later publication by Brackmann et al[48] including 6 cases of CRC in CD was unable to reproduce these findings. In contrast again, a nationwide survey from the Netherlands identified late diagnosis of inflammatory bowel disease to be associated with early development of CRC.[49] In that study, median time from diagnosis of CD to CRC was 13.6 years. In total, 30% of the patients developed CRC within 8 years after diagnosis of CD and this subgroup was of significantly more advanced age at the time of diagnosis of CD. In our cohort the patients had median disease duration of 26 years until development of CRC. Two patients developed CRC within 10 years after diagnosis of CD, which is a bit faster than reported in some studies,[48,50] but much less than in the nationwide survey from the Netherlands.[49] These 2 patients were the oldest in our cohort at the time of diagnosis of CD with the age of 44 and 59, respectively.

The risk for developing CRC in patients with CD is increased, as is the risk for an unfavorable outcome. Yet up to now no specific risk factors could be identified in CD patients. Our data suggest that CRC with a mucinous and/or signet ring cell component is far more common in patients with CD than in other sporadic CRC. In conjunction with the results of MSI analysis, this is of particular interest as the lack of MSI in patients with CRC in CD indicates that MAC in CD represents an own biological entity that warrants further investigation.

## REFERENCES


1. Eaden J. Review article: colorectal carcinoma and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2004;20(suppl 4):24–30.
2. Sebastian S, Hernandez V, Myrelid P, et al. Colorectal cancer in inflammatory bowel disease: results of the 3rd ecco pathogenesis scientific workshop (i). *J Crohn Colitis*. 2014;8:5–18.
3. Persson PG, Karlen P, Bernell O, et al. Crohn's disease and cancer: a population-based cohort study. *Gastroenterology*. 1994;107:1675–1679.
4. Mellemkjaer L, Johansen C, Gridley G, et al. Crohn's disease and cancer risk (Denmark). *Cancer Causes Control*. 2000;11:145–150.
5. Averboukh F, Ziv Y, Kariv Y, et al. Colorectal carcinoma in inflammatory bowel disease: a comparison between Crohn's and ulcerative colitis. *Colorectal Dis*. 2011;13:1230–1235.
6. Baars JE, Looman CW, Steyerberg EW, et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol*. 2011;106:319–328.
7. Bewtra M, Kaiser LM, TenHave T, et al. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. *Inflamm Bowel Dis*. 2013;19:599–613.
8. Symonds DA, Vickery AL. Mucinous carcinoma of the colon and rectum. *Cancer*. 1976;37:1891–1900.
9. Kang H, O'Connell JB, Maggard MA, et al. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. *Dis Colon Rectum*. 2005;48:1161–1168.
10. Hyngstrom JR, Hu CY, Xing Y, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the national cancer data base. *Ann Surg Oncol*. 2012;19:2814–2821.
11. Svrcek M, Cosnes J, Beaugerie L, et al. Colorectal neoplasia in Crohn's colitis: a retrospective comparative study with ulcerative colitis. *Histopathology*. 2007;50:574–583.
12. Choi PM, Zelig MP. Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention. *Gut*. 1994;35:950–954.
13. Malvi D, Vasuri F, Mattioli B, et al. Adenocarcinoma in Crohn's disease: the pathologist's experience in a tertiary referral centre of inflammatory bowel disease. *Pathology*. 2014;46:439–443.
14. Shin US, Yu CS, Kim JH, et al. Mucinous rectal cancer: effectiveness of preoperative chemoradiotherapy and prognosis. *Ann Surg Oncol*. 2011;18:2232–2239.
15. Sengul N, Wexner SD, Woodhouse S, et al. Effects of radiotherapy on different histopathological types of rectal carcinoma. *Colorectal Dis*. 2006;8:283–288.
16. Verhulst J, Ferdinande L, Demetter P, et al. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. *J Clin Pathol*. 2012;65:381–388.
17. Bosman FT. WHO Classification of Tumors of the Digestive System. 4th ed Lyon. IARC; 2010.
18. Ahls MG, Niedergethmann M, Dinter D, et al. Case report: intraductal tubulopapillary neoplasm of the pancreas with unique clear cell phenotype. *Diagn Pathol*. 2014;9:11.
19. Hirsch D, Camps J, Varma S, et al. A new whole genome amplification method for studying clonal evolution patterns in malignant colorectal polyps. *Genes Chromosomes Cancer*. 2012;51:490–500.
20. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. AdWMF. Aktualisierte s3-leitlinie diagnostik und therapie des m. Crohn 2014; updated german clinical practice guideline on "diagnosis and treatment of Crohn's disease" 2014. AWMF-Registriernummer: 021-004.
21. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 montreal world congress of gastroenterology. *Can J Gastroenterol*. 2005;19(suppl A):5A–36A.
22. Ikeuchi H, Nakano H, Uchino M, et al. Intestinal cancer in Crohn's disease. *Hepatogastroenterology*. 2008;55:2121–2124.
23. Hamilton SR. Colorectal carcinoma in patients with Crohn's disease. *Gastroenterology*. 1985;89:398–407.

24. Ouaïssi M, Maggiori L, Alves A, et al. Colorectal cancer complicating inflammatory bowel disease: a comparative study of Crohn's disease vs ulcerative colitis in 34 patients. *Colorectal Dis*. 2011;13:684–688.
25. Iesalnieks I, Gaertner WB, Glass H, et al. Fistula-associated anal adenocarcinoma in Crohn's disease. *Inflamm Bowel Dis*. 2010;16:1643–1648.
26. Schaffzin DM, Stahl TJ, Smith LE. Perianal mucinous adenocarcinoma: unusual case presentations and review of the literature. *Am Surg*. 2003;69:166–169.
27. Park JS, Huh JW, Park YA, et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. *Medicine (Baltimore)*. 2015;94:e658.
28. Markowitz S, Wang J, Myeroff L, et al. Inactivation of the type ii tgf-beta receptor in colon cancer cells with microsatellite instability. *Science*. 1995;268:1336–1338.
29. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science*. 1993;260:816–819.
30. Kakar S, Aksoy S, Burgart LJ, et al. Mucinous carcinoma of the colon: correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. *Mod Pathol*. 2004;17: 696–700.
31. Leopoldo S, Lorena B, Cinzia A, et al. Two subtypes of mucinous adenocarcinoma of the colorectum: clinicopathological and genetic features. *Ann Surg Oncol*. 2008;15:1429–1439.
32. Rosty C, Williamson EJ, Clendenning M, et al. Should the grading of colorectal adenocarcinoma include microsatellite instability status? *Hum Pathol*. 2014;45:2077–2084.
33. Kakar S, Smyrk TC. Signet ring cell carcinoma of the colorectum: correlations between microsatellite instability, clinicopathologic features and survival. *Mod Pathol*. 2005;18: 244–249.
34. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138:2073–2087. e3.
35. Inamura K, Yamauchi M, Nishihara R, et al. Prognostic significance and molecular features of signet-ring cell and mucinous components in colorectal carcinoma. *Ann Surg Oncol*. 2015;22:1226–1235.
36. Mekenkamp LJ, Heesterbeek KJ, Koopman M, et al. Mucinous adenocarcinomas: Poor prognosis in metastatic colorectal cancer. *Eur J Cancer*. 2012;48:501–509.
37. Debunne H, Ceelen W. Mucinous differentiation in colorectal cancer: molecular, histological and clinical aspects. *Acta Chir Belg*. 2013;113:385–390.
38. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF). S3-Leitlinie Kolorektales Karzinom. 2014; Registrierungsnummer: 021-007OL. German S3-guidelines colorectal cancer.
39. Messerini L, Ciantelli M, Baglioni S, et al. Prognostic significance of microsatellite instability in sporadic mucinous colorectal cancers. *Hum Pathol*. 1999;30:629–634.
40. Arai T, Kasahara I, Sawabe M, et al. Microsatellite-unstable mucinous colorectal carcinoma occurring in the elderly: comparison with medullary type poorly differentiated adenocarcinoma. *Pathol Int*. 2007;57:205–212.
41. Parham D. Colloid carcinoma. *Ann Surg*. 1923;77:90–105.
42. Börger ME, Gosens MJ, Jeuken JW, et al. Signet ring cell differentiation in mucinous colorectal carcinoma. *J Pathol*. 2007;212:278–286.
43. Catalano V, Loupakis F, Graziano F, et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. *Br J Cancer*. 2009;100:881–887.
44. Negri FV, Wotherspoon A, Cunningham D, et al. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. *Ann Oncol*. 2005;16: 1305–1310.
45. Hugen N, Verhoeven RH, Lemmens VE, et al. Colorectal signet-ring cell carcinoma: benefit from adjuvant chemotherapy but a poor prognostic factor. *Int J Cancer*. 2015; 136:333–339.
46. Statistisches Bundesamt. Diagnosedaten der Patienten und Patientinnen in Krankenhaeusern, 2014. German Federal Statistical Office. Diagnostic data of patients in hospitals, 2014. © Statistisches Bundesamt, Wiesbaden 2015.
47. Ekbom A, Helmick C, Zack M, et al. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet*. 1990;336:357–359.
48. Brackmann S, Andersen SN, Aamodt G, et al. Relationship between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. *Scand J Gastroenterol*. 2009;44: 46–55.
49. Baars JE, Kuipers EJ, van Haastert M, et al. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. *J Gastroenterol*. 2012;47: 1308–1322.
50. Lutgens MW, Vleggaar FP, Schipper ME, et al. High frequency of early colorectal cancer in inflammatory bowel disease. *Gut*. 2008;57:1246–1251.